Using cerebroplacental ratio in non-SGA infants to predict adverse perinatal outcome: caution is required

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The CPR is the ratio of the fetal Middle Cerebral Artery Pulsatility index (MCA PI) to the Umbilical Artery Pulsatility index (UA PI) with gestation specific reference centiles available.[1 2] A low CPR is now generally accepted as a proxy for late fetal growth restriction (FGR).[3 4] In late FGR (≥32 weeks) whilst the UA PI increases as gestation advances, it is uncommon for the PI to become elevated beyond the

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normal range as this only occurs with major placental vascular dysfunction.[5] Regardless of the gestation at which FGR develops, alterations in fetal cardiac output and cerebral autoregulation result in a decrease of the MCA PI and reflects fetal adaptation to suboptimal placental function, a phenomenon also known as 'brain sparing'. A low CPR is associated with a range of adverse pregnancy outcomes including stillbirth, admission to the Neonatal Intensive Care Unit (NICU), acidosis, composite neonatal morbidity and emergency operative birth for intrapartum fetal compromise.[6 7 8]

A recent Delphi survey of experts recommended the following to define late FGR (≥32 weeks): CPR <5th centile, abdominal circumference (AC) <10th centile or estimated fetal weight (EFW) <10th centile or crossing centiles of more than 2 quartiles on non-customized growth charts.[9] Indeed, some professional bodies now incorporate consideration of the CPR when making decisions regarding appropriate surveillance and/or timing of birth in cases of late onset small for gestational age (SGA) or FGR[10] as it is believed to be a better test for predicting adverse perinatal outcomes than its individual UA and MCA Doppler components.

The diagnosis of late FGR is crucially important because infants with true growth restriction as opposed to being constitutional SGA differ fundamentally in their correlation with perinatal outcomes. Whilst true FGR is a pathological condition associated with a myriad of adverse outcomes, constitutionally small infants are generally at lower risk of complications. In high income countries >60% of non-anomalous SGA births occur at term with clear evidence that reduced birthweight is associated with an increased risk of morbidity and mortality.[11, 12,13] SGA at term is a significant risk factor for stillbirth (OR 3.5 95% CI 1.8-6.7), neonatal death (OR 2.6 95%CI 1.8-3.6) and serious neonatal morbidity (OR 1.8 95% CI 1.7–1.8)[12] compared to non-SGA infants. The increased risk is likely partly due to the proportion of SGA infants that are growth restricted. However, complicating this scenario is the increasing recognition that a proportion of fetuses with estimated weights >10th centile may in fact have suboptimal growth and that this may be reflected by an abnormal CPR.[3] These infants are also at increased risk of operative

birth and neonatal morbidity. Although infants with late onset FGR only rarely demonstrate overt UA Doppler abnormalities, deterioration in the fetal condition in these cases can occur rapidly and without warning.

Given the association with adverse outcomes seen in SGA infants, the CPR is now increasingly being incorporated by obstetricians into the management of pregnancies where the fetus is not SGA. Because fear of stillbirth strongly drives obstetric management, a single low CPR alone close to term is frequently being used to justify obstetric intervention (elective early term birth and/or operative delivery) in this non-SGA cohort. This issue is compounded by the fact that in some jurisdictions, the CPR is routinely reported or easily calculable from the MCA and UA Doppler indices on the ultrasound report. Given the natural reticence to unnecessarily prolong a pregnancy in which there may be evidence of possible deteriorating placental function (on the basis of a low CPR) many obstetricians elect for early term birth. The justification for this is self-evident – stillbirth is prevented with the birth of a live infant. The key problem with this approach is the lack of good evidence on which to base it. Although a low CPR is associated with a range of adverse outcomes, its performance as a screening test is relatively poor. The definition of an appropriate CPR threshold to use is also unclear with various investigators using 5th or 10th centile cut-offs, or 0.6765 MoM or a value of <1 or <1.1.[6] In many instances, gestation specific thresholds are not stated making interpretation of test performance figures problematic. Furthermore, much of the published data comes from retrospective studies in unselected populations of women that often had clinically indicated scans.

The context in which the CPR is measured is also important – in the setting of a known SGA fetus, a low CPR may possibly be more significant than in a fetus with an EFW >10th centile. Furthermore, despite the known association between a low CPR and intrapartum and perinatal complications, there is no randomized evidence proving that early delivery for SGA fetuses (let alone for non-SGA infants) improves outcomes.

The main outcomes associated with a low CPR in late pregnancy that have been investigated so far include mode of birth, serious composite neonatal outcome, perinatal death, low Apgar score at 5 minutes, low birthweight, NICU admission and emergency delivery for intrapartum fetal compromise.[7 8 14] However, depending on the population screened, outcomes assessed, gestation the CPR is measured and specific threshold used, its test performance figures [sensitivity, specificity, area under the receiver operating characteristic (AUROC) curve, likelihood and odds ratios etc.] have wide confidence ranges, albeit with better sensitivities seen when the CPR is utilized in a SGA population. Nevertheless, the reported positive likelihood ratios (PLR) are all <10 and in many instances <5 suggesting that at best, a low CPR in late pregnancy is associated with a small to moderate likelihood of adverse outcome, even in an SGA cohort. Indeed, in the most recent systematic review and meta-analysis by Conde-Agudelo *et al*[14] the PLR for perinatal death in pregnancies with suspected FGR was only 3.9 (95%CI 3.4-4.5). When the predictive accuracy of the CPR for any composite of adverse perinatal outcomes was analyzed, the results were equally modest - for cases of suspected early FGR: PLR 4.2 (95%CI 3.4 – 5.3) and for late FGR: PLR 2.3 (95%CI 2.0 – 2.6)].[14] Thus, whilst we acknowledge the broad association with adverse outcomes, these figures in our view do not justify the increasingly prevalent practice of recommending early term birth when a low CPR is detected either incidentally or on a single ultrasound scan or on serial scans (in the absence of any other ultrasound concerns) in a non-SGA population. Such a practice engenders considerable maternal anxiety, increased obstetric intervention and the potential for actually doing harm. Indeed, there is evidence that children born at early term gestations not only have higher rates of neonatal complications[11 15] but are also at risk for longer term adverse neurodevelopmental sequelae.[16,17, 18]

The management of late SGA/FGR is already covered by comprehensive recent reviews[19] and protocols from various professional bodies and include clear recommendations of the appropriate frequency of monitoring and timing of birth (summarized by McCowan *et al*[10]). Only the New Zealand guidelines

specifically discuss the role of the CPR in monitoring and timing of delivery. Given these recommendations (pertinent only in the setting of an SGA fetus), current practice in some quarters of incorporating the CPR (or even MCA Dopplers) when the EFW is >10th centile (unless there is also evidence of reduced AC or EFW growth velocity) into clinical management should be discouraged. There is precedence for our view – in the United States routine UA and MCA Doppler measurement in the setting of appropriate fetal growth often does not attract any insurance reimbursement as these parameters have only been shown to be of benefit in high risk populations[20] and of limited prognostic value for fetal or neonatal wellbeing.[21]

We therefore suggest that if the EFW and AC is >10th centile without evidence of reduced growth velocity and the UA PI is <95th centile for gestational age, then the MCA PI (and hence the CPR) need not be reported. At this stage, we simply do not have persuasive data of adequate strength to support either increased frequency of monitoring or early term delivery. The available evidence is not sufficiently robust to justify intervention outside of randomized trials purely on the basis of a low CPR for non-SGA infants. This practice may change in the future pending the results of ongoing trials.[22]

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